Our Case No. **13130-14**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pan et al.

Serial No.: 10/600,180

Filing Date: 6/20/2003

For: Antimicrobial Compositions, Products and Methods Employing Same

Examiner: Necholus Ogden, Jr.

Group Art Unit No.: 1751

Declaration of Michael Lynch under 37 C.F.R. § 1.132

1. My name is Dr. Michael Lynch. I am President of Third Stream Bioscience, Inc, a licensee of the pending application.

2. I have been working in the bioscience/healthcare industry for over 17 years. After earning M.S. and Ph.D. degrees at the University of Miami I received a FIRST Award from the National Institutes of Health, earned tenure and the rank of Associate Professor at Purdue University, published 30 articles in peer reviewed journals and served as principal investigator for several major research programs funded by government and industry.

3. During my career, I have been involved with either developing or assisting in the development of a number of antimicrobial compositions.

4. I am familiar with the United States patent process and the United States patent laws, and I am a co-inventor on three United States Patent Applications that are directed towards antimicrobial compositions and their uses.

5. I have read the Office Action in connection with the '180 application with a mailing date of September 14, 2007.

6. The invention of the present '180 application is related to antimicrobial compositions, products and methods of using the same.

7. Antimicrobial compositions are claimed with from about 0.2% to about 70% of certain organic acids; a calcium ion scavenger - citric acid; from about 0.1% to about 40% of an anionic surfactant mixture having a characteristic selected from the group consisting of: i. a linear alkyl chain having a chain length of from about C_4 to about C_{12} and a total hydrophilic head group size of at least about 4 Angstroms, ii. an unsaturated alkyl chain having a chain length of from about C_4 to about C_{12}, iii. a branched alkyl chain having a chain length of from about C_4 to about C_{12}, and iv. combinations thereof. The compositions do not contain an antimicrobial active. The compositions have a pH of from about 2.0 to about 4.5 and are effective for inactivating viruses.

8. During my review, I considered the knowledge of one of ordinary skill in the art as well as what Beerse (U.S. Pat. No. 6,190,695) teaches to one of ordinary skill in the art. The reference cited, U.S. Pat. No. 6,190,695, does not teach or suggest the claimed compositions.

9. Specifically, U.S. Pat. No. 6,190,695 does not disclose compositions that do not have an "antimicrobial active". This is an important aspect since certain antimicrobial actives, such as Triclosan™, have recently come under fire for their role in promoting antibacterial immunity. The compositions described in Beerse all contain an antimicrobial active.

10. There is no specific teaching in Beerse that would enable one to make the claimed compositions.

11. In addition, as one skilled in the art, the results listed in Table 4 inventors surprisingly discovered that they were able to achieve the excellent antimicrobial activity reported in table 4 on page 23 of the original specification without an "antimicrobial active".

TABLE 4- EFFICACY OF COMPOSITIONS

Liquid Composition	E. coli Log reduction Time Kill (1 min): solution & wipe	E. coli Log Reduction Immediate: Vitro skin	E. coli Log Reduction Residual: Vitro skin	Rotavirus Log Reduction Immediate: Vitro skin	Rotavirus Log Reduction Residual: Bio skin
EX 1	5	4	4	3	
EX 3	5	5	5	3	3
EX 4		3	3		
EX 7		4	4		
EX 8		4	5		
EX 9		4	4		
EX 10		3	4		
EX 11	5	3	4	2	

The compositions of the examples are listed in Table 1 and reproduced below:

Component	EX 1	EX 2	EX 3	EX 4	EX 5	EX 6	EX 7	EX 8	EX 9	EX 10	EX 11	EX 12 (Conc)
Sodium Cetyl Glyceryl Sulfonate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	15
Sodium Salt Pyrrolidone Carboxylate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5		0.5	
Gluconic Acid									1.5	1.5		15
Hydrogenated Castor Oil	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	1.0
Perfume	0.05-0.1	0.05-0.1	0.05-0.1	0.05-0.1	0.05-0.1	0.05-0.1	0.05-0.1	0.05-0.1	0.05-0.1	0.05-0.1	0.05-0.1	0.5-1.0
Citric Acid anhydrous	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5		0.5		5
Malic Acid											1.5	
Methyl Cellulose		1.0										1.0
3[(2-Ethylhexyl)oxy] 1,2 Propanediol			0.5									
Benzalkonium Chloride				0.1								
Propylene Glycol					3							
2-Propanol						3						
Aloe Vera							0.1					
Menthol								0.1				
PH adjusted by 1N NaOH	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0

In contrast, those of skill in the art have generally relied upon antimicrobial actives such as Triclosan™, PCMX, or benzalkonium chloride for enhanced antimicrobial performance. As can be seen in Table 4, superior performance was achieved with examples not containing an antimicrobial active.

12. In particular, the log reduction values of the compositions versus Rotavirus are unexpected results since such non-enveloped viruses are particularly difficult to disinfect. The very high residual log reduction of both bacteria and virus is also unexpected. Furthermore, the only present FDA supported agent with a major degree of persistence is iodine/iodophors.

13. I am not aware of a previous use of compositions without an antimicrobial active that achieve such antimicrobial activity.

14. Other attempts to produce antimicrobial compositions with the performance of the claimed compositions have failed. For example, 3M recently attempted to get approval of Avagard (a combination of 61% ethyl alcohol and 1% chlorhexidinegluconate (CHG)) as a surgical site prep in addition to a surgical scrub. The FDA did not approve the indication due to unacceptable colony forming unit growback. See FDA NDA 21-074; http://www.fda.gov/cder/approval/ (Statistical Review supporting grant for Surgical Hand Scrub and Health-care Personnel Hand Wash, but not supporting grant for Surgical Site Preparation, attached).

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Dr. Michael Lynch

State of Florida
County of Palm Beach

Doris L. Del-Zio 10-29-07
Dor. L. Del-Zio

DORIS L DEL-ZIO
Notary Public - State of Florida
My Commission Expires Sep 4, 2010
Commission # DD 591353
Bonded By National Notary Assn.

APR 14 2000

STATISTICAL REVIEW and EVALUATION

NDA Number:	21-074
Drug Trade Name:	Avagard™ [redacted] antiseptic hand scrub
Formulation:	Avagard™ [redacted] Antiseptic Hand Scrub Chlorhexidine gluconate (CHG) 1% w/w Ethyl alcohol 61% w/w
Applicant:	3M Health Care, Inc. 3M Center, Building 275-3E-08 St. Paul, MN 55144-1000
Indications:	1. Surgical Hand Scrub 2. Health-care Personnel Hand Wash [redacted]
Statistical Reviewer:	George Rochester, HFD-725
Documents Reviewed:	Vol. 1.1-1.3, 1.30-1.50
Submission Date:	June 25, 1999
PDUFA Date:	June 25, 2000
Date Review Completed	April 14, 2000
Type of Review:	Clinical
Clinical Reviewer:	David Bostwick, HFD-520
Project Manager:	Maureen Dillon-Parker, HFD-520

TABLE OF CENTENTS

INTRODUCTION

The sponsor, 3M Health Care, Inc., submitted this application in support of NDA-21-074 for the product Avagard™ proposed indications: (1) surgical hand scrub; (2) health-care personnel hand wash;

Avagard™ otherwise referred to as HPD-5a in sponsor's submission and in this review, is a combination of two active ingredients: Chlorhexidine Gluconate (CHG) 1% weight per weight (w/w), ethyl alcohol 61% w/w, and formulated in an emollient rich lotion base. The inactive ingredients included in this formulation are: beheneth 10, behanyl alcohol, C20-40 pareth-24, cetyl palmitate, Diisopropyl dimer dilinoleate dimethicone, gylcerin, polyethylene glycol, squalane, and water. Both active ingredients of HPD-5a, namely, CHG 1% w/w and ethyl alcohol 61% w/w, are also active antimicrobials.

Since the two active ingredients in the Avagard™ formulation, namely, CHG and ethyl alcohol, are themselves active antimicrobials, this application must demonstrate that Avagard™- is superior to ethyl alcohol in obtaining the targeted $\log_{10}$ reductions in antimicrobial counts in accordance with the specifications of the Tentative Final Monograph for Health Care Antiseptic Drug Products Proposed Rule (TFM) (Federal Register, 17 June 1994, 31441-314452). However, considering that CHG could not be formulated for use by itself, the sponsor needs to show that HPD-5a is superior in bacterial count reductions when compared to the vehicle control, HPD-5b, which is the entire formulation without CHG, and to alcohol alone.

In support of the proposed indications the sponsor submitted data from three pivotal randomized, controlled, efficacy studies. Two of these studies, LIMS 7838 and LIMS 7957, are submitted in support of the surgical hand scrub indication; and 1 study, LIMS 7939, is presented in support of the claim for the health-care personnel hand wash indication.

SURGICAL HAND SCRUB STUDIES

Results of Pivotal Study (LIMS 7838)

Study Title

A Pivotal Study to Assess the Antimicrobial Effectiveness of Avagard™ as a Surgical Hand Scrub Formulation.

Primary Objective

To evaluate the effectiveness of the HPD-5a as a Surgical Hand Scrub formulation in meeting the TFM criteria for immediate and persistent reductions in the number of bacteria colony forming units (CFU) on the hands, and to demonstrate superior efficacy of the

combination test product, HPD-5a, compared to the vehicle control, HPD-5b, which is the same formulation without the CHG active ingredient.

Secondary Objectives

The secondary objectives for this study are:

1. To comparatively evaluate bacterial reductions achieved within 1 minute, and at 3 and 6 hours, post-treatment of HPD-5a compared to Hibiclens®.
2. To comparatively evaluate subjects' assessment of the skin condition of their hands after using the formulation HPD-5a compared to HPD-5b and/or Hibiclens®.

To satisfy these objectives this study will (1) comparatively evaluate HPD-5a versus Hibiclens® for bacterial reductions achieved within 1 minute, 3 hours, and 6 hours post-treatment; and (2) comparatively evaluate subjects' assessment of the skin condition of their hands. Each subject was randomized into one of three groups treatment groups: HPD-5a, HPD-5b, and Hibiclens®. The study subjects, and investigators were blinded to HPD-5a and HPD-5b assignment. The Hibiclens group could not be blinded due to the distinct application procedure and physical characteristics of Hibiclens®. The Hibiclens® arm was included in the study as a reference group. Individuals performing the bacterial enumeration were blinded to the test product used by the subject.

On Day 1, one application of the product to the hands was done, and bacterial counts at three time points were obtained at 1 minute, 3 hours, and 6 hours. The possible combination of sampling times for both hands of each subject were: 1 minute and 3-hour, 1 minute and 6-hour, or 3-hour and 6-hour. Equal numbers of subjects from each treatment group were randomly assigned to one of these three combinations of sampling schedules, and the selection of left hand or right hand for bacterial counts was also randomly permutated.

Required Elements

The test drug needs to satisfy all of the following at *in vivo* testing to establish efficacy (TFM, page 31445):

- **1 $\log_{10}$** reduction in bacterial count on each hand within 1 min after application
- bacterial count on each hand < baseline within 6 hours on the 1st day of use
- **2 $\log_{10}$** reductions on each hand within 1 min after application by the 2nd day
- **3 $\log_{10}$** reductions on each hand within 1 min of product application by the end of the 5th day.

Methods

Following a wash out period of at least 14 days, during which subjects refrained from using any topical antimicrobials or medicated soaps, lotions, shampoos, or similar products, three baseline measurements of bacterial flora were made. Subjects enrolled in the study had a baseline bacterial population of $\geq 1.0 \times 10^5$ CFUs per hand in the first and second of three measurements. Subjects were randomized to receive either HPD-5a or Hibiclens®. Hands were randomized one combination of bacterial sampling times. The treatment period consisted of 5

consecutive days during which subjects performed a series of 11 simulated surgical hand scrub applications (once daily on Days 1 and 5, and three times daily on Days 2, 3, and 4).

Schedule of Measurements

Prior to the application of the study products, three baseline bacterial counts were taken from each hand of each subject. Then after the first hand scrub using the assigned product, the bacterial count was taken at 0 hour time (within 1 minute ± 30 seconds) or at 3 hours time point for the first hand. The bacterial count of the second hand was taken at either the 3 hour or 6 hour time points.

The study enrolled a total of 85 subjects, 34 in the HPD-5a group, 31 in the HPD-5b group, and 20 in the Hibiclens® group. All subjects enrolled in this study met the inclusion and exclusion criteria described in the protocol. Ninety-four percent (N = 80) of the enrolled subjects completed the study. The three treatment groups were similar in age, height, weight and race distribution, except that the HPD-5b group had a higher percentage of male (58%) than the other two groups (32% for HPD-5a and 35% for Hibiclens).

Reviewer's Comment

There is no reason to expect that gender would affect the performance of these products. The height, weight, race and gender distributions are reflective of the population for which this product is intended.

Protocol Deviation

One patient who was randomized to HPD-5b treatment actually received Hibiclens®.

Microbial Counts

Antimicrobial efficacy results are presented for studies LIMS 7838 and LIMS 7957 (surgical hand scrub) and 7939 (health care personnel hand wash). Log_{10} of all microbial count data from these studies are calculated. The average of the log of the three baseline bacterial counts is used to determine each hand's baseline count for Studies LIMS 7957 and 7838. Only one baseline count was taken for study LIMS 7939.

Log_{10} reductions were calculated by subtracting the post-treatment log_{10} count from the baseline log_{10} count on the same hand. Counts were recorded at times: Day 1, Day 2, and Day 5 at 1 min, 3 hr, and 6 hr for Studies LIMS 7957 and 7838; and Wash 1, Wash 3, Wash 7, and Wash 10 for the LIMS 7939 study. Each participant performed a total of 11 hand scrubs over a five day period. In the LIMS 7939 study, log counts and log reductions of both hands were averaged to obtain one value for each subject.

Measurements that fall outside of the respective sampling window as specified in the protocol are included in the analysis, since there were no gross departures from the protocol. In addition to summaries of the individual studies, a combined summary is presented for the log-transformed bacterial counts and log reductions for the HPD-5a and Hibiclens® treatment arms for the LIMS 7957 and LIMS 7838 studies taken together. Hibiclens® is included as an internal control and is used primarily as an aid for interpreting the study conduct and results.

The difference in log reductions between HPD-5a v. HPD-5b (Study LIMS 7838 only) and HPD-5a v. Hibiclens® (Studies LIMS 7957, 7838, and 7939) are analyzed for each microbial count measurement by a two sample t-test. Summary tables present the difference in the log reduction, a 95% CI around the difference in the log reduction, and the p-value for each

treatment pair for each microbial count measurement. To ensure congruence between the CI and the p-value (i.e., so that the CI will not contain zero when the p-value is significant), the t-distribution will be used to construct the confidence intervals.

Safety

Five subjects (080, 010, 042, 066, 075) reported adverse events. Subjects 066 and 075 withdrew from the study due to an upper respiratory condition and a accidental injury, respectively. These events were determined to be unrelated to the study drug. Subject 042 experienced conjunctivitis for 13 days and blurred vision for 2 days after rubbing his eye following product application to his hands. These adverse events resolved spontaneously without apparent long term sequelae.

Reviewer's Comment for Efficacy (LIMS 7838)

As shown in Table 1, the baseline bacterial counts were approximately 6 log_{10} CFUs. There were 34 patients randomized to HPD-5a, 20 to Hibiclens® and 31 to HPD-5b. During the LIMS 7838 study, one patient was randomized to the HPD-5b treatment group, but actually received Hibiclens®. Sampling for bacterial counts were performed at 1 minute and 3 hours, 1 minute and 6 hours, or 3 hours and 6 hours. Because each subject can fall into only one sampling schedule the sample sizes reflected in the body of Table 1 are smaller than the numbers of subjects originally randomized to the respective treatments.

These results show that Avagard™ [redacted] is superior to HPD-5b, the entire formulation without the CHG. Avagard™ [redacted] achieved or exceeded the required elements specified in the TFM. FDA and sponsor's results were identical.

Chlorhexidine 1% w/w component was not tested by itself in this study because attempts at making this formulation without alcohol was unsuccessful.

APPEARS THIS WAY ON ORIGINAL

Table 1. **Log_{10} Reductions in Bacterial Counts (CFU/Hand) and Log_{10} Reduction Differences from Baseline Counts among HPD-5a and HPD-5b and Hibiclens, at 1 Minute, 3-hours and 6-hours over the 5 Day Study Period, based on the LIMS 7838 Surgical Hand Scrub Study for Treatment Groups as Randomized**

Day/Time Point	HPD-5a (N=34)	Hibiclens (N=20)	HPD-5b (N=31)	P-value** (95% CI)
Baseline Period Mean log_{10} Counts	**6.1**	**6.0**	**6.0**	**N/A**
Day 1, Log Reduction				
N	21	13	21	
1 min	2.6	1.6	1.1	**0.0004**
95% CI	(1.9, 3.3)	(0.7, 2.5)	(0.4, 1.8)	(0.49, 2.42)
N	23	14	21	
3 hr	3.1	1.8	1.4	< 0.0001
95% CI	(2.7, 3.6)	(1.2, 2.4)	(1.0, 1.8)	(1.19, 2.24)
N	24	13	20	
6 hr	2.8	1.4	0.5	**< 0.0001**
95% CI	(2.3, 3.2)	(0.8, 1.9)	(0.2, 0.8)	(1.73, 2.85)
Day 2, Log Reduction				
N	21	13	20	
1 min	3.2	2.4	2.0	**< 0.0001**
95% CI	(2.9, 3.6)	(2.1, 2.8)	(1.7, 2.3)	(0.75, 1.70)
N	21	14	21	
3 hr	3.7	2.3	1.3	< 0.0001
95% CI	(3.3, 4.0)	(1.7, 2.9)	(0.9, 1.8)	(1.76, 2.84)
N	22	13	20	
6 hr	3.6	2.3	0.5	< 0.0001
95% CI	(3.2, 3.9)	(1.9, 2.7)	(0.1, 1.0)	(2.46, 3.60)
Day 5, Log Reduction				
N	20	13	20	
1 min	3.5	3.6	1.5	**< 0.0001**
95% CI	(3.1, 3.9)	(3.1, 4.1)	(1.1, 1.9)	(1.12, 2.47)
N	21	13	20	
3 hr	3.9	3.6	1.4	< 0.0001
95% CI	(3.7, 4.2)	(3.2, 4.0)	(1.0, 1.8)	(1.86, 2.87)
N	21	12	18	
6 hr	3.5	3.0	0.5	< 0.0001
95% CI	(3.2, 3.8)	(2.3, 3.7)	(0.1, 0.9)	(2.48, 3.51)

Source: Sponsor's Appendix Tables 2A and 3A. ** P-values for comparing HPD-5a v HPD-5b.

Reviewer's Comment for Safety (LIMS 7838)

A statement to the effect of "Not to be used on the face" and instructions on what actions to take in case of accidental contact with conjunctiva might be useful in the labeling of this product. Include a statement to the effect that should this product come in contact with the eyes, rinse immediately with plenty of "cold" water and contact a physician if the user experiences blurred vision for more than 2 days and/or severe irritation of the eyes for greater than 72 hours.

Certainly this product should not be used by children, a population especially prone to such accidental contamination of the eyes. This is necessary since it will be used by health-care personnel in pediatric institutions where it is common practice for children and family members to use health-care personnel hand scrubs/washes especially when entering intensive care and special isolation units (such as transplant units). No additional safety concerns are noted.

RESULTS OF PIVOTAL STUDY (LIMS 7957)

Study Title

To assess the antimicrobial effectiveness of surgical hand scrub formulation.

Objectives

The secondary objectives were:

(1) to comparatively evaluate bacterial reductions achieved within 1 min and at 3 and 6 hr post-treatment, HPD-5a vs. Hibiclens®;
(2) to comparatively evaluate the subjects' assessment of the skin condition of their hands after treatment with HPD-5a compared to Hibiclens®.

Design

LIMS 7957 was a prospective, randomized, evaluator-blinded, parallel arm study to evaluate the effectiveness of the products as surgical hand scrub in producing an immediate and persistent reduction in the normal bacterial flora of the hand based on the TFM and ASTM- E (1991).

Fifty-two subjects were enrolled in the study, 27 randomized to Avargard™, [redacted] and 25 to Hibiclens®. All subjects enrolled in this study met the inclusion and exclusion criteria described in the protocol. Forty-eight of 52 (92%) patients completed the study. No protocol violations were noted. Other aspects of study design and conduct were identical to study LIMS 7838. Baseline means were comparable between treatment groups.

Reviewer's Comments for Efficacy (LIMS 7957)

Results for the HPD-5a and Hibiclens® treatment groups are presented in Table 2 and are identical to results displayed in sponsor's Table 8. Based on the data presented for LIMS 7957, the following conclusions can be drawn concerning antimicrobial effectiveness:

1. *HPD-5a met or exceeded TFM (Federal Register, 17 June 1994) criteria for antimicrobial effectiveness as a surgical hand scrub.*

2. *HPD-5a was equal or superior to Hibiclens® in antimicrobial effectiveness, as assessed by log reductions in counts of hand bacteria.*
3. *Both HPD-5a and Hibiclens met the required elements specified in the TFM for antimicrobial effectiveness of surgical hand scrub formulations.*

Table 2. **Log Reductions in Bacterial Counts (CFU/Hand) and Log Reduction Differences Between HPD-5a and Hibiclens® for Surgical Hand Scrub Formulation based on the LIMS 7957 Study**

Day/Time Point	HPD-5a (N=27)	Hibiclens® (N=25)	Log Reduction Difference	P-value** (95% CI)
Baseline Period Mean*	**6.3**	**6.4**	**N/A**	**N/A**
Day 1 Log Reduction				
1 min	2.5	1.8	0.65	0.0095
(95% CI)	(2.1, 2.9)	(1.5, 2.1)		(0.17, 1.13)
6 hr	2.2	1.9	0.25	0.3989
(95% CI)	(1.6, 2.7)	(1.6, 2.3)		(-0.35, 0.86)
Day 2 Log Reduction				
1 min	3.0	2.6	0.44	0.1546
(95% CI)	(2.5, 3.5)	(2.2, 2.9)		(-0.17, 1.05)
Day 5 Log Reduction				
1 min	3.7	3.7	0.00	0.9974
(95% CI)	(3.3, 4.1)	(3.3, 4.1)		(-0.54, 0.54)

* This is the mean of all three baseline counts. ** HPD-5a vs. Hibiclens®

Safety

Three episodes of adverse events were reported among three subjects (001, 020, 047). Subject 001 experienced a maculo-papular rash that was likely due to the test product. Duration of episode was 23 days. No significant action was needed to resolve these events and no long term sequelae noted. Subjects 020 and 047 withdrew from the study due to menorrhagia and a viral infection, respectively. These events were assessed as most likely unrelated to the study drug.

Reviewer's Comments for Safety (LIMS 7957)

One of 27 (3.7%) subjects enrolled in this study experienced a maculo-papular rash of 23 days duration. This rash was most likely attributed to use of Avargard™ Discontinuation of use of this product was sufficient to allow for resolution of the rash. A cautionary statement about not applying product to areas of the skin where there is disruption of skin integrity is useful for the consumer information sheet. There were no other safety concerns raised from this study.

LIMS 7838 and LIMS 7957 Combined Analysis

Based on the combined data from LIMS 7838 and 7957, descriptive statistics are provided for log counts and log reductions at each use where measurements were recorded. Ninety-five percent confidence limits based on the t-distribution are provided for log reductions.

HPD-5a vs. Hibiclens®

At all Day 1 and Day 2 time points, mean log reductions were significantly higher in the HPD-5a treatment group compared to Hibiclens®. The differences between the HPD-5a and Hibiclens® treatment group was statistically significant on Day 5 at 6 hr, but not at Day 5 1 min or Day 5 at 3 hr.

Table 3 Log Reductions in Bacterial Counts (CFU/Hand) and Log Reduction Differences Between HPD-5a and Hibiclens® in LIMS 7957 and 7838 Combined Analysis for Surgical Hand Scrub Indication

Day/Time Point	HPD-5a (N=61)	Hibiclens® (N=44)	Log Reduction Difference	P-value** (95% CI)
Baseline Period Mean*				
	6.2	6.2	N/A	N/A
Day 1, Log Reduction				
1 min	2.5	1.7	0.80	0.0083
95% CI	(2.1,3.0)	(1.3,2.1)		(0.30, 1.43)
6 hr	2.5	1.7	0.80	0.0005
95% CI	(2.2,2.9)	(1.4,2.0)		(0.37, 1.31)
Day 2, Log Reduction				
1 min	3.1	2.5	0.60	0.0035
95% CI	(2.8,3.4)	(2.2,2.7)		(0.26, 1.05)
6 hr	3.5	2.3	1.20	<0.0001
95% CI	(3.2,3.7)	(2.1,2.6)		(0.81, 1.48)
Day 5, Log Reduction				
1 min	3.6	3.6	0.00	0.4435
95% CI	(3.3,3.9)	(3.3,3.9)		(-0.40, 0.39)
6 hr	3.6	3.3	0.30	0.0416
95% CI	(3.4,3.9)	(2.9,3.7)		(-0.06, 0.77)

* This is the mean of all three baseline counts.

Reviewer's Comment for Efficacy (Combined)

Table 3 showed that the log reductions for HPD-5a was significantly greater for HPD-5a compared to Hibiclens® at all sampling times except at Day 5 at 1 minute. More importantly this analysis shows that both HPD-5a and Hibiclens met the requirements for bacterial counts reductions as specified in the TFM. Figure 1 also showed that both HPD-5a and Hibiclens exceeded the required bacterial reductions.

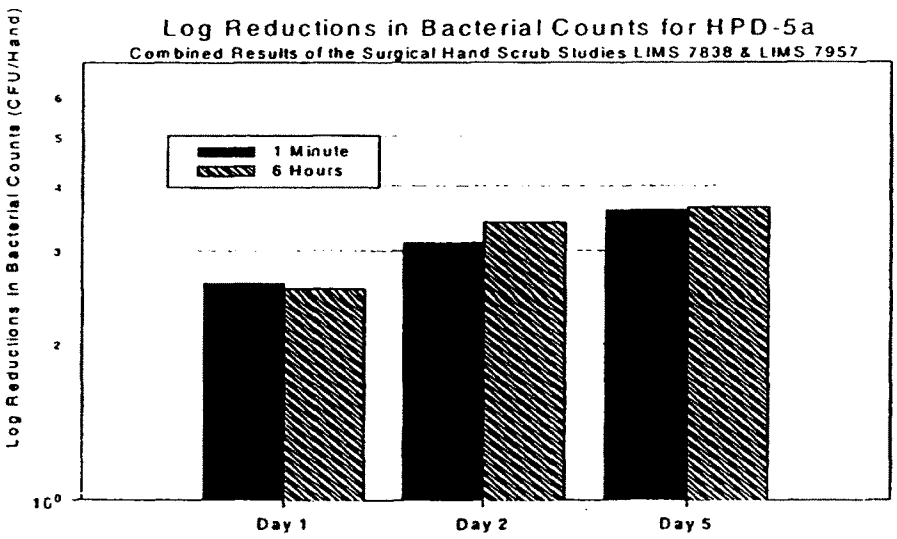


Figure 1. Time at which Bacterial Counts were obtained

Both hand scrub studies evaluated the hand condition via a self-assessment scale. It is difficult to interpret the validity of these measurements by using a such a scale. It would have been preferred to have a professional make these post-therapy assessments using well defined criteria which would increase the reliability and validity of these measures.

HEALTH-CARE PERSONNEL HAND WASH STUDY

Results of the Pivotal Study (LIMS 7939)

Study Title

Pivotal study to assess the antimicrobial effectiveness of health-care personnel hand was formulations.

Objective

The objective of this study is to evaluate the antimicrobial effectiveness of the investigational Health-care Personnel Hand Wash (HPD-5a) in producing an immediate and persistent reduction in transient bacteria on the hands as specified in the TFM and the ASTM, Standard 1174-94 (1996).

Forty-eight subjects met the enrollment criteria and completed the study as specified in the protocol. Twenty four subjects were randomized to each treatment.

Method

Following a 7 days washout period during which stabilization of normal bacterial flora is expected a 1 day test period in which each subject performed 10 hand washes. Following an initial, otherwise called the practice wash, with bland soap, subjects' hands were contaminated with a suspension of *Serratia marcescens*, a marker organism that is a common soil contaminant. The baseline sample was taken after the first contamination to determine the number of marker organisms which survive on the hands. Both hands were re-contaminated prior to each wash with test products.

Post-treatment sampling for bacterial counts were done after the 1st, 3rd, 7th and 10th washes. Changes from baseline bacterial counts obtained with the test material were determined and compared with changes from baseline bacterial counts obtained with the reference product. Since the antiseptic formulations were identifiable by participants the product to which each participant could not be masked. However, the microbiologists who performed the bacterial enumeration were blinded to the study treatment.

TFM Criteria for Health-Care Personnel Antiseptic Formulations

The TFM criteria for health-care personnel hand wash are:

(1) 2 $\log_{10}$ reduction of the artificially applied microbes (CFU/hand) within 5 minutes after completing the 1st wash, **and**
(2) 3 $\log_{10}$ reductions of the artificially applied microbes (CFU/hand) within 5 minutes after completing the 10th wash.

Hibiclens, a currently approved product, was used as a reference control formulation.

Efficacy

The primary efficacy measure was the $\log_{10}$ reduction of bacteria CFU/hand following treatment after the 1st and 10th applications.

Safety

There were no adverse events reported during the conduct of this study.

Results

The mean $\log_{10}$ reduction of bacterial counts for HPD-5a v. Hibiclens® and test of differences in counts are summarized in Table 4. The mean reduction of bacterial counts for HPD-5a after the 1st Wash was 2.1 log reductions (2.57 for Hibiclens®) and 3.74 log reductions after the 10th Wash (3.7 log reductions for Hibiclens®).

Table 4. **Log Reductions in Bacterial Counts (CFU/Hand) and Log Reduction Differences Between HPD-5a and Hibiclens® for LIMS 7939 Health-Care Personnel Hand Wash Study**

Day/Time Point	HPD-5a (N=24)	Hibiclens® (N=24)	Log Reduction Difference	P-value** (95% CI)
Baseline Period Count	7.0	7.0	N/A	N/A
Wash 1, Log Reduction				
5 min	2.14	2.57	-0.43	0.0051
(95% CI)	(1.9, 2.4)	(2.4, 2.8)		(-0.72,-0.14)
Wash 10, Log Reduction				
5 min	3.74	3.70	0.04	0.8567
(95% CI)	(3.3, 4.2)	(3.4, 4.0)		(-0.45, 0.54)

Reviewer's Comment for Efficacy (LIMS 7939)

As shown in Table 4, HPD-5a met the criteria of at least 2.0 log reductions after the 1st Wash, and 3 log reductions after the 10th Wash. HPD-5a satisfied the TFM efficacy requirement for health-care personnel hand wash.

Reviewer's Comment for Safety (LIMS 7939)

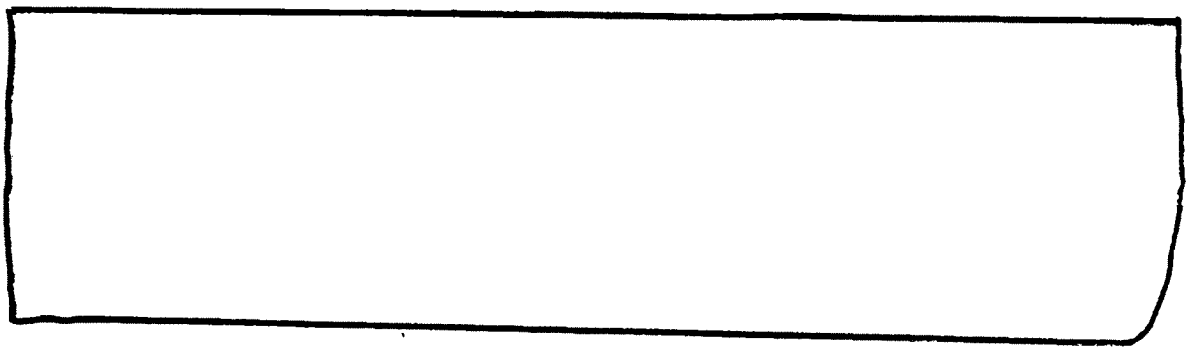
There were no safety issues raised from this study.

REVIEWER'S OVERALL SUMMARY FOR EFFICACY

1. *Avargard™ [redacted] met the TFM criteria for efficacy for surgical hand scrub formulations in reducing bacterial counts by one log_{10} reduction at 1 minute on Day 1; 2 log_{10} reductions of counts at 1 minute on Day 2; and 3 log_{10} reductions at Day 5 at 1 minute compared to baseline.*
2. *Results from the LIMS 7838 study show that Avargard™ [redacted] is superior to the vehicle, HPD-5b, and alcohol alone at all the required sampling times specified in the TFM. Chlorhexidine 1% w/w component was not tested in this study because attempts at making this formulation without alcohol was unsuccessful.*
3. *Both hand scrub studies evaluated the hand condition via a self-assessment scale. It is difficult to interpret the validity of these measurements by using a such a scale. It would have been preferred to have a professional make these post-therapy*

assessments using well defined criteria which would increase the reliability and validity of these measures.

4. *Results from the LIMS 7939 study show that HPD-5a met the TFM criteria for health-care personnel hand wash of at least 2.0 log reductions in bacterial counts after the 1st Wash, and 3 log reductions after the 10th Wash compared to baseline.*



REVIEWER'S OVERALL SUMMARY FOR SAFETY

A caution might be included in the label to the effect, "Not to be used as a facial wash/scrub" and in case of such accidental exposure to the eyes "rinse at once with plenty of cold water. Contact a physician if the user experiences blurred vision for more than 2 days and/or severe irritation of the eyes for greater than 72 hours."

Certainly this product should not be used by children, a population especially prone to such accidental exposure to the eyes/face. Since it will be used by personnel in pediatric institutions where it is common practice for children and family members to wash with health-care personnel hand washes/scrubs, especially in intensive care and isolation units (such as transplant units), these warnings are necessary for the end user. No additional safety concerns are noted.

RECOMMENDATIONS

1. **Use as a Surgical Hand Scrub: RECOMMEND APPROVAL**

The test formulation, Avargard™ [redacted] met the TFM Criteria for efficacy as an Antiseptic Hand Scrub formulation.

2. **Use as a Health-care Personnel Hand Wash: RECOMMEND APPROVAL**

The test formulation, Avargard™ [redacted] met the TFM Criteria for the Health-care Personnel Antiseptic Formulation.

[redacted]

REFERENCES

Federal Register Part III, Tentative Final Monograph for Health-Care Antiseptic Drug Products; Proposed Rule (TFM). Vol. 59, No. 116, (Friday, June 17, 1994). Code of Federal Regulations, Title 21 CFR Parts 333 and 369.

American Society for Testing and Materials (ASTM) Standard 1174-94 (1996). Standard Test Method for Evaluation of Health-Care Personnel Hand wash Formulations. Annual Book of ASTM Standards, Vol. 11.05., pp. 480-482.

ASTM-E (1991) Standard Test Method for Evaluation of Surgical Hand Scrub Formulations, 1115-91.

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